REMARKS

Reconsideration of the rejections set forth in the Office action mailed October 8, 2003 is respectfully requested, for the reasons discussed below. Claims 1-27 are currently pending. No amendments are made with this response.

I. The Invention

The applicant's invention, as embodied in independent claim 1, provides a method of separating a population of duplexes comprising different oligomeric analyte molecules which are substantially uncharged. Each analyte molecule is able to hybridize with a specific charged probe molecule, which is a nucleic acid or a fully charged nucleic acid analog. Accordingly, each duplex comprises one charged strand and one substantially uncharged strand. The method comprises the steps of:

(a) applying the different analyte molecules (substantially uncharged) and the specific probe molecule (fully charged) to a charge-bearing separation medium, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof; and

(b) separating the duplexes from each other and from single stranded species within the medium.

It is the discovery of the applicants that the duplexes of the different (substantially uncharged) analyte molecules with the specific (charged) probe molecule can be separated in a charge-bearing separation medium. The charged-based separation is believed to arise from the differing amounts of unconstrained single stranded charged probe molecule in the different duplexes. See, for example, the discussion at page 9 of the specification, with reference to Figs. 3-4. This method permits separation of the substantially uncharged oligomers without the use of the extreme pH ranges described in the prior art.

II. Rejections under 35 U.S.C. §102(b)

Claims 1-2 and 27 were rejected under 35 U.S.C. §102(b) as being anticipated by Summerton *et al.*, U.S. Patent No. 5,405,928. This rejection is respectfully traversed for the following reasons.

Examiner's Characterization of Reference Teachings

The Examiner asserts that the reference teaches that "duplex oligomeric analyte molecules...are made of uncharged backbones...as explicitly taught by Summerton *et al.* in the abstract". The applicants find this statement to be inaccurate, for the following reasons:

The '928 patent describes a "polymer composition" which is effective to bind to a "duplex polynucleotide" or "duplex nucleic acid" (see Title and Abstract). As stated in the Abstract of the reference, the polymer composition has an uncharged backbone. This polymer composition is single stranded (see *e.g.* Fig. 34, and various descriptions of the polymer, including the synthesis description in Example 8).

The "duplex polynucleotide" or "duplex nucleic acid" to which the "polymer composition" binds is, according to various descriptions in the reference, a duplex nucleic acid in a biological setting or in a sample derived from biological tissues, typically DNA. (See, for example, column 6, lines 10-12: "For many *in vivo* applications of sequence-specific duplex-directed nucleic acid-binding agents, the principal target is DNA". See also column 43, lines 36-40: "In many applications, the *in situ* hybridization is directed toward a target sequence in a double-stranded duplex nucleic acid, typically a DNA duplex associated with a pathogen or with a selected sequence in chromosomal DNA."; and column 44, lines 26-31: "Another general application of the polymer invention is for isolating duplex nucleic acid structures from a nucleic acid mixture, such as a mixture of genomic fragments, a blood sample containing a selected viral duplex, or a mixture of plasmids with different duplex inserts in different orientations.")

Accordingly, the reference describes the binding of an uncharged "polymer composition", which is single stranded (see *e.g.* Fig. 34, as noted above) to a charged duplex nucleic acid or polynucleotide. Such binding would thus form a triplex (see *e.g.* column 28, line 62), consisting of the uncharged binding polymer and the double stranded, charged nucleic acid molecule.

Lack of Anticipation

Nowhere does the reference teach step (a) of claim 1, namely:

(a) applying to a charge-bearing separation medium a mixture of (i) different (substantially uncharged) analyte molecules and (ii) a specific (charged) probe molecule, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof.

A "probe-analyte duplex" of applicants' claim 1 will include one substantially uncharged strand (that is, an analyte molecule) and one charged strand (that is, the charged probe molecule). Moreover, the charged probe molecule is the same in each duplex ("a specific probe molecule"). Such duplexes are not shown or suggested in the reference, which, as discussed above, describes either fully charged duplexes (*i.e.* nucleic acids) or triplexes.

Nor does the reference show or suggest, expressly or "inherently", the application to any medium of a mixture of different uncharged molecules and a specific charged molecule.

The method embodied by claim 19 of the reference, to which the Examiner refers (page 3 of Office Action), entails contacting a "sample" which contains a "duplex nucleic acid having a selected target sequence" with the "polymer composition of claim 1", *i.e.* the uncharged-backbone molecule, "having a subunit sequence effective to bind...with the selected target sequence".

This method is further described at column 44, lines 25-50 of the reference. As described therein, the method is useful for "isolating duplex nucleic acid structures from a nucleic acid mixture, such as a mixture of genomic fragments, a blood sample containing a selected viral duplex, or a mixture of plasmids with different duplex inserts" (emphasis added). Such "mixtures" clearly contain various different charged species, not a "specific charged probe molecule" as in applicants' claims.

Moreover, the uncharged-backbone polymer, that is, the binding polymer, is described as follows: "The binding polymer used in the method is (a) designed for base-specific binding to a selected target duplex sequence....The binding polymer is added to the sample material and incubated under conditions which allow binding of the polymer to its target sequence". This

description clearly suggests a single "binding polymer", that is, a single uncharged-backbone sequence, not the "different oligomeric [substantially uncharged] analyte molecules" of the applicants' claim.

Inherency

The Examiner refers to "inherency" in making this rejection. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991); both cases cited in *In re Robertson*, 169 F.3d 743, 49 USPQ2d 1949 (Fed. Cir. 1999).

Therefore, inherency could not be established by an assertion that the method of claim 19 in the reference could employ "different oligomeric analyte molecules, wherein said molecules are composed of linked subunits of which at least 90% are uncharged", as recited in the applicants' claim. To establish inherency, the feature must be necessarily present and recognizable as such by persons of ordinary skill.

The claimed feature--*i.e.* application of a population of different, substantially uncharged analyte molecules to a separation medium--is clearly not necessarily present in the method of claim 19 of the reference. Since the method of claim 19 is used for the isolation of "a selected target sequence", one would not typically use more than one type of "binding polymer" in carrying out the method. Accordingly, to one skilled in the art, it would not even be considered a typical feature of the method.

In view of the above, the disclosure of the reference does not show the elements of independent claim 1, expressly or inherently. Accordingly, the applicants request that the rejection under 35 U.S.C. §102(b) be withdrawn.

III. Rejections under 35 U.S.C. §103(a)

Dependent claims 3-6, 10, 12-13, 15 and 18-26 were rejected under 35 U.S.C. §103(a) as being obvious over Summerton *et al.*, U.S. Patent No. 5,405,928, discussed above, in view of Summerton *et al.*, U.S. Patent No. 5,034,506. This rejection is respectfully traversed for the following reasons.

In making the 103(a) rejection, the Examiner repeatedly refers to portions of the specification (*i.e.*, Example 19, Column 33, lines 22-39, Example 20, Column 34, lines 22-29, and Example 21, Column 35, lines 41-49 and Figure 16) which were discussed by the applicants in the previous response and in the telephonic interview of August 29th, 2003, when this patent was asserted as the primary reference. As pointed out by the applicants in that discussion, these portions of the patent describe the determination of binding of a synthesized oligomer to its complementary DNA, where binding is measured spectrophotometrically (see *e.g.* column 34, lines 45-69). This method of characterization employs a solution containing a single uncharged oligomer and one or more DNA molecules (including the complementary DNA; *e.g.*, column 33, line 24). There is clearly no motivation provided to apply such a solution to a "separation medium", no suggestion that any duplexes could be separated in a separation medium, and no motivation to include multiple, different uncharged oligomers.

The Examiner also refers to another passage which was discussed in the August 29th interview, *i.e.* Column 12, line 65 to column 13, line 6 (page 7 of Office Action). This passage describes separation of different uncharged oligomers on an ion exchange column. As pointed out previously, there is no suggestion, nor would there be any reason, to include a charged nucleic acid probe molecule in such a procedure, or to attempt to separate any duplexes on the column. Because the separation is carried out at high or low pH, in order to ionize the bases of the uncharged oligomers, as stated in the reference (see column 12, lines 42-48), no duplexes could stably form under the conditions of separation (as pointed out, for example, in the comments by inventor Dwight Weller forwarded by fax on August 28, 2003).

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art,

to modify a reference or combine reference teachings. The prior art must also provide a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. (MPEP §2143)

For the reasons discussed above, the primary ('928) reference does not show or suggest the method of independent claim 1. For the reasons discussed in the previous response and in the telephonic interview of August 29th, 2003, the '506 reference does not show or suggest the method of independent claim 1. Because elements of the independent claim (*e.g.* step (a)) are not shown by either reference, the references in combination cannot suggest the claimed method.

In view of the foregoing, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

IV. Further Rejections under 35 U.S.C. §103(a)

Other rejections under this section were made as follows:

Claims 7- 9 and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Connolly *et al.* (U.S. Patent No. 6,342,370).

Claim 16 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.* (U.S. Patent No. 6,263,286).

Claim 17 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.*, above, and further in view of Hearn *et al.* (U.S. Patent No. 4,279,724).

These rejections are essentially identical to those made in the Office Actions of January 24, 2003 and June 3, 2003, with the addition of the disclosure of the Summerton '938 patent. The rejections are respectfully traversed in light of the following remarks.

The Summerton references, U.S. Patent Nos. 5, 405,938 and 5,034,506, are discussed above. These references in combination do not suggest of the method of independent claim 1 and its advantages over conventional separations of substantially uncharged oligomers. To reiterate, the present invention is based on the discovery that duplexes of different substantially uncharged

analyte molecules with a specific charged probe molecule can be separated from each other on a charge-bearing separation medium.

The secondary references were cited for their disclosure of various individual features of dependent claims 2-27, and they were discussed, as follows, in the response filed on September 3, 2003.

Connolly *et al.* is cited for the disclosure of polynucleotides containing deletion variant sequences. The polynucleotides are nucleic acids, such as RNA or DNA (see column 3, lines 29 and 60-62 of the reference). They are clearly not "composed of linked subunits of which at least 90% are uncharged". The polynucleotide can be used as probes for diagnosis of disorders related to mutations in the DNA of an individual (*e.g.* column 2, lines 46-50). There is no suggestion of forming duplexes of the variant polynucleotides with a charged probe molecule and separating the duplexes.

Gilmanshin *et al.* is cited for the disclosure of fluorescent labeling and the use of electrophoresis. Both of these techniques are, of course, used in many different technologies, including DNA sequencing. In the sections of this reference pointed out by the Examiner, short labeled probes are used to bind to a DNA which is to be sequenced. The distance between the probes on the DNA is determined, *e.g.* by FRET (column 10, line 64 and following). The probes can then be removed from the DNA by denaturation, *e.g.* under electrophoresis (column 19, lines 14-21: "denaturation of the DNA sample...The dissociated probes are removed, *e.g.* by electrophoresis..."). The reference does not teach or suggest electrophoretic separation of duplexes.

Hearn *et al.* is cited for its disclosure of a superimposed pH gradient, for use in "preparative electrofocusing of protein mixtures" (column 1, lines 47-49). There is no discussion of oligomeric duplexes of any sort.

The teachings of these references, directed to various technologies, provide no guidance regarding a method of separating duplexes comprising different, substantially uncharged oligomeric molecules and a specific charged probe molecule. Even if the teachings of the

secondary references were combined with those of the Summerton *et al.* patents, these combined teachings would not suggest the claimed method.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

V. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

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